III. REMARKS

Claims 1, 3-5, 7-18, and 20-23 are pending in this application. By this Amendment, claims 3, 4, and 9-12 have been amended, claims 2, 6, and 19 have been cancelled, and claims 21-23 have been added. Reconsideration in view of the above amendments and the following remarks is respectfully requested.

Applicants do not acquiesce in the correctness of the rejections and reserve the right to present specific arguments regarding any rejected claims not specifically addressed and to present additional arguments regarding any rejected claims that are specifically addressed. Further, Applicants reserve the right to pursue the full scope of the subject matter of the claims in a subsequent patent application that claims priority to the instant application.

Rejection of / Objection to Claims 2-6 and 8-12

In the Office Action, it is unclear whether the Examiner intends to reject or object to claims 2-6 and 8-12. No statutory basis for rejection is cited, so Applicants assume that the claims are objected to. Clarification by the Office is respectfully requested.

The Examiner alleges that claims 2 and 10-12 lack proper antecedent basis. Claim 2 has been cancelled and claims 10-12 have been amended to provide antecedent basis. Accordingly, Applicants assert that the basis for the Examiner's allegation has been obviated.

The Examiner alleges that the terms "includes" and "suitable" in claims 2-4 and 8-10 are relative terms, rendering the claims indefinite. With respect to Applicants' use of "includes" in claims 2 and 8, the Examiner alleges that its use renders the claim

scope ambiguous as to whether the claim from which it depends contains a "pharmaceutically acceptable acid addition salt form." Office Action at 2.

Claim 2 has been cancelled. With respect to claim 8, Applicants assert that the Examiner has misread or misunderstood the claims. Claim 7, from which claim 8 depends, recites in relevant part "recovering the resulting compound in free base or acid addition salt form." Claim 8 then recites "wherein the acid addition salt form includes a pharmaceutically acceptable acid addition salt form."

There is no ambiguity. The scope of claim 7 includes all acid addition salt forms, whether pharmaceutically acceptable or otherwise. That is, the acid addition salt forms may be entirely pharmaceutically acceptable salt forms, entirely non-pharmaceutically acceptable salt forms, or a combination of the two. Claim 8 further narrows this scope, such that the acid addition salt form includes a pharmaceutically acceptable acid addition salt form. That is, the scope of claim 8 is narrower, excluding acid addition salt forms consisting entirely of non-pharmaceutically acceptable salt forms.

Thus, Applicants assert that the use of "includes" in claim 8 introduces no ambiguity into the scope of claim 8 or claim 7. Accordingly, Applicants respectfully request withdrawal of the objection.

With respect to Applicants use of "suitable" in claims 3, 4, 9, and 10, the Examiner states that "[what is] suitable for one person may not be suitable for another" and alleges that it is unclear whether the recitation "is the innate nature of the biological activity or a 'therapeutically effective amount' of the compound in a composition for therapeutic use." Office Action at 2.

Without conceding the correctness of the Examiner's position and to provide greater clarity, each of claims 3, 4, 9, and 10 has been amended to replace "suitable" with "useful." To the extent that the Examiner may view these claims as "essential duplicates" of claims 1 and 7, from which they depend, Applicants will respond to any double-patenting rejection the Office may issue upon allowance of claims 1 or 7.

Applicants assert, therefore, that the above amendments and arguments overcome the objections to the claims. Accordingly, Applicants respectfully request that the objections be withdrawn.

35 USC 112 Rejection

In the Office Action, claims 7-12 are rejected under 35 USC 112(1) as allegedly not enabling the recited "pharmaceutical composition." This rejection is respectfully traversed.

Applicants note that paragraphs [0023] through [0028], for example, describe pharmaceutical uses of the compound of the invention and, in particular, pharmaceutical compositions comprising the compound of the invention and a pharmaceutical carrier or diluent. Accordingly, Applicants assert that claims 7-12 are enabled with respect to the recited "pharmaceutical composition" and respectfully request that the rejection be withdrawn.

35 USC 103 Rejection

In the Office Action, claims 1-6 are rejected under 35 USC 103(a) as allegedly unpatentable over US Patent No. 5,364,866 to Strupczewski et al. in view of Corbett et

al., *Iloperidone: Preclinical Profile and Early Clinical Evaluation*, CNS Drug Reviews, 3 (2):120-147 (136) (1997), Caccia, *Biotransformation of Post-Clozapine Antipsychotics*, Clinical Pharmacokinetics 38(5):393-414 (401) (2000), or Subramanian et al., *Receptor profile of P88-8991 and P95-12113, metabolites of the novel antipsychotic iloperidone*, Progress in Neuro-Psychopharmacology & Biological Psychiatry 26:553-560 (559) (2002) and Garattini, *Active Drug Metabolites: An Overview of their Relevance in Clinical Pharmacokinetics*, Clinical Pharmacokinetics 10:216-227 (1985), further in view of Bundgaard, DESIGN OF PRODRUGS, 1-3 (1985) and Waller et al., *Prodrugs*, British Journal of Clinical Pharmacology 28:497-507 (1989). This rejection is respectfully traversed.

The Office states that Strupczewski et al. disclose the "composition of the parent drug iloperidone and its composition which is tantamount to a claim to all its metabolite." Office Action at 3. Applicants disagree.

Applicants do not dispute that the claimed compound is an active metabolite of iloperidone. Neither do Applicants dispute that esterification of drugs having a hydroxyl or carboxyl group is a prodrug design strategy that is sometimes useful. However, such a strategy is not always helpful and it could not, therefore, have been predicted *a priori*, with a reasonable expectation of success, that an esterified form if iloperiodone would have useful prodrug properties.

Waller et al., relied on by the Office, disclose two major rationales for prodrug formulations: 1) to solve pharmaceutical problems (e.g., unpalatability, gastrointestinal irritation, pain on injection, poor solubility) and 2) to solve pharmacokinetic problems, specifically a) to achieve more complete or predictable absorption, b) to reduce

incomplete and variable systemic bioavailability, c) to improve access to the site of action, d) to activate selectively a drug in the intended target tissue, and e) to optimize either the rate of onset or duration of action of a drug. *See* Waller et al. at 498.

Thus, there are many possible effects that use of a prodrug formulation can have. The actual effect or effects of a given prodrug strategy, however, cannot be predicted for a particular active. "This review has considered some of the prodrugs currently available. They demonstrate *varying degrees of success* in achieving the goals of prodrug design." Waller et al. at 504 (emphasis added). "Prodrugs have *partially* fulfilled their promise in clinical practice...*Theoretical benefits have not always shown convincing improvements in practice*." *Id.* at 505 (emphasis added).

In the instant case, Applicants discovered that the ester cleavage of fatty acid ester derivatives of the P-88-8991 metabolite in fact does proceed slowly. This is a result which could have been hoped for, but not predicted.

Applicants assert that claim 1-6 are not obvious in view of Strupczewski et al., Corbett et al., Caccia et al., Subramanain et al. or Garattini et al., whether considered individually or in any combination. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Double-Patenting Rejection

In the Office Action, claims 1-12 are provisionally rejected on the grounds of non-statutory obviousness-type double patenting as allegedly unpatentable over claims 1-3 of co-pending US Patent Application No. 12/403,755 in view of Corbett et al., Caccia et

al. or Subramanian et al. and Garattini et al. further in view of Bungaard and Waller et al. This rejection is respectfully traversed.

The Examiner states that "[t]he same rational *[sic]* as delineated in [the 35 USC 103(a) rejection] is also applicable and hereby incorporated by reference." Office Action at 3. Accordingly, Applicants assert that claims 1-12 are allowable for the reasons given above and respectfully request that the rejections be withdrawn.

Conclusion

In view of the foregoing, Applicants respectfully request withdrawal of the rejections and allowance of the application. Should the Examiner require anything further from Applicants, the Examiner is invited to contact Applicants' undersigned representative at the number listed below.

Respectfully submitted,

/Stephen F. Swinton, Jr./ 05 August 2010

Stephen F. Swinton, Jr. Date
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